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RESEARCH ARTICLE

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Preoperative prognostic nutritional index predicts survival of patients with intrahepatic cholangiocarcinoma after curative resection

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Background: Intrahepatic cholangiocarcinoma (ICC) is an aggressive malignancy. We sought to examine the association between preoperative prognostic nutritional index (PNI) and long-term overall survival among patients with ICC who underwent curative-intent resection.

Methods: Patients who underwent hepatectomy for ICC between 1990 and 2015 were identified using an international multi-institutional database. Clinic-pathological characteristics and long-term outcomes of patients with PNI ≥ 40 and <40 were compared using univariable and multivariable analyses.

Results: Among 637 patients, 53 patients had PNI < 40 (8.3%) and 584 patients had PNI ≥ 40 (91.7%). While there was no difference between PNI groups with regard to tumor size ($P = .87$), patients with PNI < 40 were more likely to have multifocal

disease (PNI < 40, n = 16, 30.2% vs PNI ≥ 40, n = 65, 11.1%; $P < 0.001$), poorly differentiated or undifferentiated ICC (PNI < 40, n = 13, 25.5% vs PNI ≥ 40, n = 75, 13.1%; $P = 0.020$) and T2/T3/T4 disease vs patients with PNI ≥ 40 (PNI < 40, n = 38, 71.7% vs PNI ≥ 40, n = 265, 45.4%; $P < 0.001$). Patients with PNI ≥ 40 had better OS vs patients with PNI < 40 (5-year OS: PNI ≥ 40: 47.5%, 95% CI, 42.2 to 52.6% vs PNI < 40: 24.6%, 95% CI, 12.1 to 39.6%; $P < 0.001$). On multivariable analysis, PNI < 40 remained associated with increase risk of death (HR, 1.71; 95% CI, 1.15 to 2.53; $P = 0.008$).

Conclusion: A low preoperative PNI was associated with a more aggressive ICC phenotype. After controlling for these factors, PNI remained independently associated with a markedly worse prognosis.

KEYWORDS

intrahepatic cholangiocarcinoma, lymphocytes, nutritional index, surgery

1 | INTRODUCTION

The incidence of intrahepatic cholangiocarcinoma (ICC) in the Western world is approximately 1 to 2 per 100 000 people per year.[2] ICC accounts for 3% of all gastrointestinal cancers and is the second most common primary liver cancer.[3] While surgical resection offers the best opportunity for long-term survival, long-term outcomes are generally poor. To this point, even among patients with early stage disease who undergo curative-intent liver resection, 5-year overall survival (OS) ranges from 20% to 35%.[4] Traditionally, the American Joint Committee on Cancer (AJCC) staging system has been used to determine patient prognosis for ICC.[5,6] However, the AJCC staging system relies only on standard clinic-pathologic criteria, which may not always accurately risk-stratify patients with ICC. Therefore, novel methods of accurately determining individual patient-specific prognosis based on clinical, biological, and genetic factors have been proposed.[1,7-10] In turn, these factors may be incorporated into traditional clinical tools for predicting long-term patient outcomes, as well as guide the choice of appropriate treatment strategies.[11,12]

The prognostic nutritional index (PNI) is a simple marker of individual nutrition and inflammation levels based on serum albumin concentration and total lymphocyte count, both of which can be easily obtained with routine preoperative blood tests.[13] Several studies have demonstrated that PNI can be used as a prognostic indicator in patients with various malignancies including nasopharyngeal carcinoma, small-cell lung cancer, esophageal, and pancreatic cancer.[14-22] The objective of the current study was to utilize a multi-institutional international database to examine the association between preoperative PNI and long-term OS outcomes among patients with ICC who underwent curative-intent resection.

2 | METHODS

2.1 | Study population

A multi-institutional database from 14 major hepatobiliary centers in the United States, Europe, Australia, and Asia was used to identify patients who underwent curative-intent liver resection for ICC from 1990 to 2015. Patients for whom perioperative data on serum albumin concentration and total lymphocyte count were unavailable, patients with concurrent extrahepatic disease at the time of hepatectomy, and patients who underwent incomplete resection with a macroscopic positive margin (R2) were excluded. The study was approved by the institutional review boards of the participating institutions. Patient demographic information was obtained, including patient age and gender. Preoperative serum albumin concentration and total lymphocyte count were obtained for each patient. PNI was calculated as 10×serum albumin (g/dL) + 0.005×total lymphocyte count per mm^3. Based on established criteria, a threshold value of 40 was used to discriminate patients with low (PNI < 40) vs normal (PNI ≥ 40) PNI.[23-25] Clinical data were collected on American Society of Anesthesiologists (ASA) Physical Status, Hepatitis B virus (HBV) and Hepatitis C virus (HCV) infection status, the presence of cirrhosis, preoperative carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9), and the administration of neo-adjuvant chemotherapy. The extent of the hepatectomy with or without lymphadenectomy was determined in addition to any other additional procedures (eg major vascular, bile duct, or inferior vena cava resection). Hepatic resections were classified according to the Brisbane 2000 classification.[26] Major hepatectomy was defined as the resection of three or more segments, while minor hepatectomy was defined as the resection of two or fewer segments according to the Couinaud classification or nonanatomic wedge resections.[27] Histopathological reports were used to determine tumor characteristics including the size; multifocality; morphologic type; histologic grade; presence of biliary, perineural, or vascular invasion; extent of lymph node involvement; any liver capsule involvement or extension to other organs; and the margin status. Tumor stage, nodal stage, and overall cancer stage were determined according to the American Joint Committee on Cancer (AJCC) eighth edition staging system.[28] A multiphasic abdominal or pelvic computed tomography or magnetic resonance imaging with IV contrast and chest CT every 6 months for 2 years then annually up to 5 years was the standard follow-up protocol after surgical resection.

TABLE 1 Clinic-pathological characteristics for patient groups based on PNI (n = 637)

Variables	PNI < 40	PNI ≥ 40	*P* value
Patients (N)	53 (8%)	584 (92%)	
Gender			0.34
Male	30 (56.6%)	369 (63.3%)	
Female	23 (43.4%)	214 (36.7%)	
Age, median (IQR)	64 y (56-71)	57 y (49-64)	<0.001
ASA score			<0.001
1-2	21 (39.6%)	425 (72.8%)	
3-4	32 (60.4%)	159 (27.2%)	
Underlying liver disease			0.09
Cirrhosis	3 (7.0%)	87 (16.8%)	
None	40 (93.0%)	431 (83.2%)	
Neoadjuvant chemotherapy			<0.001
No	32 (74.4%)	510 (92.4%)	
Yes	11 (25.6%)	42 (7.6%)	
Ca 19-9, median (IQR)	62 U/mL (13-398)	44 U/mL (17-204)	0.15
CEA, median (IQR)	2.2 ng/mL (1-4)	2.5 ng/mL (2-4)	0.79
Type of resection			0.003
Wedge resection	38 (71.7%)	286 (49.1%)	
Minor hepatectomy	11 (20.8%)	158 (27.1%)	
Major hepatectomy	4 (7.5%)	139 (23.8%)	
Margins			0.005
Negative	43 (81.1%)	537 (92.4%)	
Positive	10 (18.9%)	44 (7.6%)	
Size			0.87
≤5 cm	21 (39.6%)	238 (40.7%)	
>5 cm	32 (60.4%)	346 (59.3%)	
Lesion			<0.001
Unifocal	37 (69.8%)	519 (88.9%)	
Multifocal	16 (30.2%)	65 (11.1%)	
Liver capsule involvement			0.46
Not present	43 (81.1%)	496 (84.9%)	
Present	10 (18.9%)	88 (15.1%)	
Microvascular invasion			0.64
Not present	38 (73.1%)	442 (76.0%)	
Present	14 (26.9%)	140 (24.0%)	
Major vascular invasion			0.21
Not present	44 (83.0%)	518 (88.8%)	
Present	9 (17.0%)	65 (11.2%)	
Perineural invasion			<0.001
Not present	34 (68.0%)	475 (87.2%)	
Present	16 (32.0%)	70 (12.8%)	
Direct involvement of adjacent organs			0.04
No	47 (88.7%)	557 (95.3%)	
Yes	6 (11.3%)	27 (4.7%)	
Grade			0.02
Well-moderate	38 (74.5%)	497 (86.9%)	
Poorly differentiated-undifferentiated	13 (25.5%)	75 (13.1%)	
Lymphadenectomy			0.01
No	34 (64.2%)	463 (79.3%)	
Yes	19 (35.8%)	121 (20.7%)	
AJCC eighth edition *T* stages			<0.001
T1a/T1b	15 (28.3%)	319 (54.6%)	
T2/T3/T4	38 (71.7%)	265 (45.4%)	

(Continues)

TABLE 1 (Continued)

Variables	PNI < 40	PNI ≥ 40	*P* value
AJCC eighth edition *N* stages			0.99
N0	5 (26.3%)	32 (26.5%)	
N1	14 (73.7%)	89 (73.5%)	
AJCC eighth edition stages			0.24
Ia/Ib/II	2 (10.5%)	27 (22.3%)	
IIIa/IIIb	17 (89.5%)	94 (77.7%)	
Adjuvant chemotherapy			0.07
No	29 (61.7%)	424 (73.7%)	
Yes	18 (38.3%)	151 (26.3%)	

AJCC, American Joint Committee on Cancer; IQR, inter-quartile ranges; PNI, prognostic nutritional index.

2.2 | Statistical analysis

Continuous variables were reported as sample medians with inter-quartile ranges (IQR), while categorical variables were reported as whole numbers and percentages. Overall survival (OS) was defined as the time between the date of surgery and the date of death, and living patients were censored at the date of last follow-up. The survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazards models were used to evaluate any association among variables and survival outcomes, with coefficients reported as hazard ratios (HR) and corresponding 95% confidence intervals (CI). All tests were two sided, and a $P < 0.05$ was considered statistically significant. All analyses were performed using STATA version 12.0 (StataCorp, College Station, TX).

3 | RESULTS

3.1 | Demographic variables

Among 637 patients who underwent liver resection for ICC, the median preoperative albumin level was 4.1 g/dL (IQR, 3.8 to 4.5) and the total lymphocyte count was 1614 cells/mm^3 (IQR, 1140 to 2197). Serum albumin was < 3.5 g/dL in 72 patients (11.3%) and 22 patients (3.5%) had a low-lymphocyte count (<800 lymphocytes/mm^3); 53 patients had PNI < 40 (8.3%) and 584 patients had PNI ≥ 40 (91.7%). There were clinical differences among patients with a low PNI (< 40) vs high PNI (≥40) (Table 1). Specifically, patients with PNI < 40 were older than patients with PNI ≥ 40 (median age: PNI < 40, 64 years, IQR 56 to 71 vs PNI ≥ 40, 57 years, IQR 49 to 64; $P < 0.001$); patients with PNI < 40 were also more likely to have an ASA ≥ 3 vs patients with a PNI ≥ 40 (PNI < 40, n = 32, 60.4% vs PNI ≥ 40, n = 159, 27.2%; $P < 0.001$). While there was no difference between PNI groups with regard to tumor size ($P = .87$), patients with PNI < 40 were more likely to have multifocal disease (PNI < 40, n = 16, 30.2% vs PNI ≥ 40, n = 65, 11.1%; $P < 0.001$) and less likely to undergo major hepatectomy vs PNI ≥ 40 patients (PNI < 40, n = 4, 7.5% vs PNI ≥ 40, n = 139, 23.8%; $P = 0.003$). In addition, patients with PNI < 40 were more likely to have poorly or undifferentiated ICC (PNI < 40, n = 13, 25.5% vs PNI ≥ 40, n = 75, 13.1%; $P = 0.020$) and invasion of adjacent organs (PNI < 4,0 n = 6, 11.3% vs PNI ≥ 40, n = 27, 4.7%; $P = 0.04$) vs patients with PNI ≥ 40. Patients with PNI < 40 were also more likely to have T2/T3/T4 disease compared with patients who had PNI ≥ 40 (PNI < 40, n = 38, 71.7% vs PNI ≥ 40, n = 265, 45.4%; $P < 0.001$); however, the incidence of N1 disease between the two groups was similar ($P = 0.99$). Post-operatively, 48.1% (n = 25) of patients with PNI < 40 had a complication compared with 34.1% (n = 199) of PNI ≥ 40 patients ($P = 0.044$).

3.2 | Survival analysis: Impact of PNI on long-term outcomes

On univariable analysis several factors were associated with patient prognosis. Specifically, CEA and CA 19-9 serum values, margin status, major vascular invasion, number of ICC, tumor size, tumor differentiation, as well as T and N AJCC stages were each associated with OS (all $P < 0.05$) (Table 2). Of note, on univariable analysis, PNI was also associated with OS as patients with PNI ≥ 40 had a better OS compared with patients who had PNI < 40 (5-year OS: PNI ≥ 40: 47.5%, 95% CI, 42.2 to 52.6% vs PNI < 40: 24.6%, 95% CI, 12.1 to 39.6%; $P < 0.001$). On multivariable analysis, several factors remained associated with OS. In particular, patients with N1 disease had more than a three-fold increased risk of death compared with patients who had N0 disease (N0: patients references; N1: HR, 3.07, 95% CI, 1.45 to 6.49; NX, HR, 2.13, 95% CI, 1.05 to 4.34; both $P < 0.05$). Margin status was associated with long-term prognosis, as patients with a positive margin (R1) had a 69% increased risk of death compared with R0 patients (HR 1.69, 95% CI, 1.13 to 2.55; $P = 0.010$); T3/T4 disease (HR 1.28, 95% CI, 0.98 to 1.66; $P = 0.065$) and a poorly/undifferentiated ICC (HR 1.47, 95% CI, 1.05 to 2.04; $P = 0.023$) also impacted OS. In addition, after controlling for other competing risks, patients with PNI < 40 had a 71% increased risk of death vs patients with ≥ 40 (HR, 1.71; 95% CI, 1.15 to 2.53; $P = 0.008$). A sensitivity analysis including only patients who underwent liver resection after 2004 (n = 595, 93.4%) confirmed the results of the analyses performed on the whole cohort (5-year OS: PNI ≥ 40, 48.7%; 95% CI, 43.1–53.9% vs PNI < 40, 33.6%; 95% CI: 17.1–50.9%; $P = 0.004$) (Supporting Information Figure S1). In the sensitivity analysis, after controlling for other competing risks,

TABLE 2 Univariate analysis of prognostic predictors of 5-y overall survival

Variables	5-y OS (%)	95% CI	*P*
Gender			.29
Male	41.9	35.5-48.1	
Female	52.6	44.5-60.0	
Age			.53
<75 y	45.4	40.2-50.4	
≥75 y	48.3	27.4-66.5	
ASA score			.62
1-2	44.9	38.6-51.0	
3-4	46.3	37.7-54.5	
Neoadjuvant chemotherapy			.38
No	47.1	41.6-52.4	
Yes	59.6	41.9-73.6	
Ca 19-9, U/mL			<0.001
<50	54.6	46.6-61.8	
≥50	35.0	27.6-42.5	
CEA, ng/mL			<0.001
<10	48.2	41.5-54.5	
≥10	6.2	0.5-22.9	
Type of resection			.39
Wedge resection	38.0	27.1-48.8	
Minor hepatectomy	49.1	39.3-58.1	
Major hepatectomy	46.9	40.0-53.5	
Margins			0.002
Negative	47.1	41.8-52.2	
Positive	31.8	16.6-48.1	
Size, cm			<0.001
≤5	60.8	52.6-68.0	
>5	35.0	28.8-41.2	
Lesion			<0.001
Unifocal	48.8	43.4-54.0	
Multifocal	24.3	13.9-36.1	
Liver capsule involvement			.88
Not present	44.8%	39.1-50.3	
Present	48.6%	37.2-59.0	
Microvascular invasion			0.037
Not present	47.6%	41.9-53.1	
Present	37.8%	27.5-48.1	
Major vascular invasion			<0.001
Not Present	47.9%	42.5-53.1	
Present	25%	11.7-40.8	
Perineural Invasion			0.046
Not Present	47.0%	41.5-52.2	
Present	22.8%	9.1-40.2	
Invasion of adjacent organs			<0.001
No	47.6%	42.3-52.5	
Yes	11.6%	2.3-29.4	
Grade			0.005
Well—Moderate	47.8%	42.2-53.0	
Poorly—Undifferentiated	31.1%	19.3-43.8	
AJCC 8th edition T Stages			<0.001
T1a	68.0%	57.8-76.3	
T1b	38.3%	28.6-47.9	
T2	32.3%	23.3-41.7	
T3	57.8%	45.1-68.6	
T4	11.6%	2.3-29.4	

(Continues)

TABLE 2 (Continued)

Variables	5-y OS (%)	95% CI	P
AJCC 8th edition N Stages			<0.001
N0	70.0%	47.8-84.1	
N1	25.2%	13.2-39.2	
Nx	47.7%	42.1-53.1	
AJCC 8th edition Stages			0.039
Ia	100.0%	–	
Ib	68.6%	21.3-91.2	
II	59.9%	27.8-81.5	
IIIa	–	–	
IIIb	25.9%	13.6-40.0	
PNI			<0.001
≥40	47.5%	42.2-52.6	
<40	24.6%	12.1-39.6	
Adjuvant chemotherapy			0.29
No	48.6%	39.3-57.2	
Yes	45.6%	39.4-51.7	

AJCC, American Joint Committee on Cancer.

patients with PNI < 40 had a 58% increased risk of death vs patients with ≥40 (HR, 1.58; 95% CI, 1.01 to 2.49; $P = 0.049$) (Table 3).

4 | DISCUSSION

The identification of preoperative factors with prognostic value is important as such information may inform surgical decision making, more accurately stage patients than anatomic data alone, and guide the use of adjuvant or neoadjuvant therapies. Recent studies have focused on the value of nutritional and inflammatory biomarkers in clarifying the prognosis of patients undergoing curative-intent surgery for cancer. As it reflects both an individual's nutritional and immunologic status, PNI, defined by albumin serum level and lymphocyte count, is therefore a potentially powerful tool in predicting long-term outcomes. To the best of our knowledge, this is the first study to explore the relationship between PNI and various clinicopathological characteristics as well as to investigate the clinical value of preoperative PNI among patients with ICC undergoing curative-intent liver resection. The results of this study demonstrate that not only a low preoperative PNI was associated with traditionally negative prognostic indicators (eg advanced age, poorer health status, advanced stage disease), but also PNI was independently associated with worse OS even after controlling for confounding factors (Figure 1).

Preoperative nutritional status, as measured by serum albumin levels, has traditionally been one of the more important prognostic indicators among patients undergoing cancer surgery. Malnutrition is relatively common among patients with primary liver cancer, which has consistently been associated with a poor prognosis.[29] For example, Nagaoka et al[30] reported a two-fold increased risk of death among patients with a low serum albumin level (<3.5 g/dL) undergoing liver resection for hepatocellular carcinoma (HCC) compared with patients who had a serum albumin level ≥3.5 g/dL ($P = .008$). Other studies have similarly reported a worse prognosis for patients with hypoalbuminemia undergoing surgery for other gastrointestinal cancers, however the association between malnutrition and long-term outcomes of patients with ICC has not been completely examined.[30-35] Albumin is a well-recognized indicator of liver function and has many important physiological functions, including the maintenance of serum osmolality, tissue repair, transport of intrinsic and extrinsic compounds like nutrients and drugs, and regulation of systemic inflammation.[36] However, a major advantage of PNI as a reliable prognostic indicator is that PNI not only directly correlates with albumin, but also reflects patient immune status.[37] In the current analysis, patients with a low albumin level (serum albumin < 3.5 g/dL, n = 72, 11%) had a decreased 5-year OS vs patients with a serum albumin ≥ 3.5 g/dL (n = 565, 89%) (5-year OS: serum albumin < 3.5 g/dL, 17% vs serum albumin ≥ 3.5 g/dL, 49%; $P < .001$). A low serum albumin translated into a 2.5-fold higher risk of death compared with patients who had a normal albumin level.

Lymphocyte count has been proposed as a clinically consistent indicator of patients' immune status and the degree of host immune response to neoplastic disease. Lymphocyte count has been included in multiple prognostic scoring systems for cancer patients, including the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR).[38-42] In particular, Lin et al[43] demonstrated that patients with lower lymphocyte counts and high NLRs who underwent hepatectomy for ICC had poor anti-tumor immunity that translated into worse OS and recurrence-free survival (RFS) compared with patients who had a normal lymphocyte count. In a separate study, Omichi et al[1] reported that among 43 patients treated with preoperative chemotherapy for ICC, 5-year OS and RFS were 95% and 70%, respectively, among patients with NLR < 3.0 vs 5-year OS and RFS of 50% and 26%, respectively, among patients with NLR ≥ 3.0 (both $P \leq .004$). In the current analysis, 5-year OS was 36% for patients

TABLE 3 Multivariable survival analysis of prognostic predictors of overall 5-year survival

Variables	HR	95% CI	*P* value
Margins			0.010
Negative	–	–	
Positive	1.69	1.13-2.55	
Grade			0.023
Well-moderate	–	–	
Poorly-undifferentiated	1.47	1.05-2.04	
AJCC eighth edition T Stages			0.065
T1a/T1b/T2	–	–	
T3/T4	1.28	0.98-1.66	
AJCC eighth edition N stages			
N0	–	–	0.003
N1	3.07	1.45-6.49	0.038
NX	2.13	1.05-4.34	
PNI			0.008
≥40	–	–	
<40	1.71	1.15-2.53	

AJCC, American Joint Committee on Cancer.

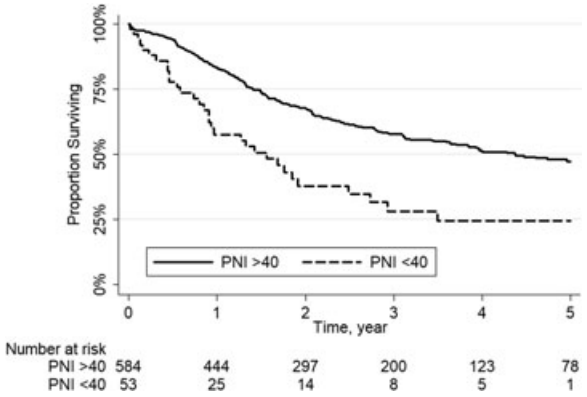

FIGURE 1 Kaplan-Meier curve comparing overall survival among patients with PNI ≥ 40 vs PNI < 40. PNI, prognostic nutritional index

who had a low lymphocyte count (< 800 lymphocytes/μL) compared with 46% for patients with a lymphocyte count ≥ 800 lymphocytes/μL, resulting in a 82% increased risk of death among patients with a low lymphocyte count compared with normal levels ($P < 0.001$). Given the apparent importance of the host immune response and the increased interest in using immunotherapy for biliary tract cancers, further research evaluating the role of lymphocyte count, as well as other markers of immune status, in predicting prognosis and guiding treatment options is warranted.[41,44-46]

The finding that a low PNI was associated with traditional markers of disease aggressiveness is consistent with previous studies.[47,48] A recent meta-analysis of 4756 patients with ICC observed that many features of advanced tumors, including size, tumor number, lymph node metastasis, vascular invasion, and poor tumor differentiation were associated with decreased OS.[4] In the current study, low PNI was strongly associated with many adverse prognostic factors including multifocal disease, differentiation, and perineural invasion ($P < 0.05$). The association between low PNI and an aggressive tumor phenotype might be attributed to a poor immunological and nutritional condition. In turn, patients with a PNI < 40 had a 5-year OS of only 25%, while patients with a PNI ≥ 40 had a 5-year OS of 48% ($P < 0.001$). Of note, in a multivariable model after adjusting for adverse features such as tumor number, grade of ICC differentiation, and AJCC T and N stages, PNI remained associated with OS. Specifically, patients with a PNI < 40 had a 71% increased risk of death compared with patients with a PNI ≥ 40. The data suggest that preoperative PNI may be a relevant clinical predictive indicator of aggressive ICC biology and may warrant including PNI into the routine preoperative evaluation.[49]

Several limitations should be considered when interpreting the results of the current study. Given the retrospective design, there likely was some selection bias especially since only patients who underwent surgery were included in the analytic cohort. Therefore, it may be possible that more patients with ICC have a low PNI, but these patients had more aggressive ICC phenotype and were not considered for surgery. In the current analysis, the cut-off value of 40 to discriminate patients with low (PNI < 40) and normal (PNI ≥ 40) values of PNI as suggested by Onodera et al.[23-25] However, several other studies have suggested other PNI cut-off values ranging between 40 and 51.[50-52] Data on hematological malignancies, active infections, or inflammatory disease were also not available and may influence PNI levels. Moreover, neoadjuvant and adjuvant therapies might differently influence the prognosis of patients in the high and low PNI level groups. Even though both neoadjuvant and adjuvant therapies were not associated with OS in the whole cohort or in the high and low PNI level groups (all $P > 0.10$) further studies should investigate whether a low PNI level should be included as an indication for perioperative treatments.

In conclusion, in an international, multi-institutional cohort of patients with ICC undergoing hepatic resection, a low preoperative PNI was associated with a more aggressive ICC phenotype characterized by more advanced disease on presentation. After controlling for these factors, PNI remained independently associated with a markedly worse OS. Future studies should evaluate the nutritional, inflammatory, and immunologic mechanisms underlying this association. PNI may be a clinically meaningful tool to stratify patient prognosis, as well as identify patients at highest risk of poor outcomes after curative intent surgery for ICC thereby informing decisions about adjuvant therapy.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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